IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Ulf TILSTAM, et. al.

Group Art Unit: 1623

Serial No.: 09/471,040

Examiner: Howard V. Owens

Filed: December 23, 1999

For: PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE LITHIUM, SODIUM, POTASSIUM, CALCIUM AND MAGNESIUM SALTS AND PURIFICATION PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE AND FLUDARABINE-PHOSPHATE WITH A PURITY OF AT LEAST 99.5%

DECLARATION UNDER C.F.R. §1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ulf Tilstam, being duly warned, declare that: I am a citizen of Belgium, residing at De Grunne laan 40, B-1970 Wezembeek Oppem, Belgium.

I possess the degree of a Doctor of Natural Sciences, having studied Chemistry at the Royal Institute of Technology in Stockholm, Sweden.

Between March 1, 1990 and August 31, 2002, I had been employed as a Chemist by Schering, Aktiengesellschaft, Berlin, Germany.

I am a member of the Royal Society of Chemistry, the American Chemical Society, the German Chemical Society and the Swedish Chemical Society.

I am an inventor of the above-captioned application and am, therefore, familiar with the invention described therein and with the grounds of rejection in view of U.S. Patent No. 4,357,324 (Montgomery) made against the claims of the application in the Office Action mailed January 2, 2003 from the U.S. Patent and Trademark Office. Under German law I will receive royalties as an inventor once the patent issues because this invention is commercialized.

Under my supervision, process experiments using lithium, sodium, potassium, calcium and magnesium salts were conducted for the production of a pure fludarabine-phosphate (active ingredient in Fludara® (Berlex Labs, wholly owned U.S. subsidiary of

Schering AG)) compound having a purity of at least 99.5% (see Examples 2 to 5). Heretofore, such purity could not be achieved for fludarabine-phosphate.

As explained in the specification at the paragraph bridging pages 1-2 (and DE 19543052A1 discussed below), conventional methods for producing fludarabine-phosphate require reacting starting materials and crystallizing the resulting fludarabine-phosphate in water. Effective temperatures for the crystallizations are approximately 75°C, which destroys a portion of the fludarabine-phosphate upon cooling due to its thermal instability in water. Thus, conventional purification techniques cannot be applied to obtain a purity of 99.5% or greater because such purifications are again performed under such aqueous conditions, which creates additional impurities.

Crystallizations of fludarabine-phosphate in organic solvents, such as dimethyl formamide, acetonitrile, and many others, to avoid the use of water have been attempted. However, a different, solid form of fludarabine-phosphate was always obtained.

Moreover, Montgomery does not resolve this problem. Particularly, Montgomery exemplifies the production of fludarabine-phosphate by lyophilization. See example 2 at column 4. However, lyophilized fludarabine-phosphate is an amorphous compound and not the crystalline form used as drug substance. To obtain a substance suitable for use as a drug, the amorphous lyphilisate must be recrystallized. Such a recrystallization is again carried out as above, i.e., in water, which is heated to around 70°C, followed by rapid cooling to around 10°C and subsequent isolation of the crystallized material. Consequently, the fludarabine-phosphate decomposes during the recrystallization process, resulting in a lower purity as discussed in the specification.

It is not simple as presumed in the office action to purify fludarabine-phosphate, partially because of the mentioned instability. As a result, before this invention, all chemical processes used in preparation of fludarabine-phosphate yielded only a maximum purity of 97.67%, on a lab-scale or otherwise. This represents about 2.5% of impurities in a commercial drug. If it were as easy or even possible, as assumed by the examiner, to purify fludarabine-phosphate to any desired degree, why would FDA permit such a high level of impurities to be contained in a commercial drug product? Clearly it would not. This is strong evidence of the fact that conventional processes are not able to purify fludarabine-phosphate to any desired degree.

Attached is DE 19543052A1 (by the same inventors as this application) with an attached English translation. DE 19543052A1 discusses that recystallizing fludarabine-phosphate in water destroys a portion of the fludarabine-phosphate because of its thermal

instability in water. See last paragraph at page 1 of the translation. Also, this reference contains six examples all using various ion exchange resins to purify fludarabine-phosphate. In no case is the purity at least 99.5%. The results of these examples were as follows:

Example	Ion Exchange Material	% Impurity	fludarabine-phosphate purity
2	Amberlite A252C	1.24%	98.76%
3	Amberlite A252C & Charcoal	1.09%	98.91%
4	Duolite CU 33	1.57%	98.43%
5	IRC 50	1.5%	98.5%
6	AXAD-7	1.7%	98.3%
7	Dowex SOX2-200	1.2%	98.8%

Another experiment has also been performed (see the attached table (ATTACHMENT A)) depicting in detail the nature of the impurities which are involved when fludarabine-phosphate is purified with another such typical ion exchange resin, AMBERLITE IR 120. The purification was conducted, analogously to the procedures used in DE 19543052 A1, by dissolving fludarabine-phosphate of a 97.67% starting purity in a reaction vessel containing an excess amount of resin at 75° C, stirring for 8 minutes, filtering of the resin and rapidly cooling the solution to room temperature. After crystallization is the obtained product filtered and dried. Also in this case is it essential to dissolve fludarabine-phosphate in hot water, which of course causes partial degradation of the material. The degree of degradation is of course also depended upon which scale the purification is performed. The purification method using ion exchange resins could only be used on a maximum scale of 100 g fludarabine-phosphate. The purity of the filtered product was determined using HPLC. All eluted peaks were set at 100% and then the single peaks were analyzed by the conventional rule of three, to get the amount of single impurities. As can be seen, the content of many of the impurities was lowered by the ion exchange treatment, but in several cases the impurity content actually increased, due to the effects of this process. As a result, the total purity obtained was only 99.14%. The purities reported herein were determined to four significant figures, with the only uncertain digit being in the hundredths position. The precision obtained clearly demonstrates that even an error in the hundredths position of the largest degree would not cause the 99.14% value to overlap with a purity of 99.5%). The value of

99.14% represents the highest ever-achieved purity for fludarabine-phosphate (other than per the invention of this application), despite the best efforts of my research group, as outlined above, and everyone else in the field as far as I am aware.

Thus, employing best efforts using any available prior art purification technique, fludarabine-phosphate cannot be purified to an amount of 99.5% or greater as required by the claims. Rather, as explained above, only significantly lower purities are possible. It is for this reason that an entirely new and inventive preparation process, designed to avoid the need for hot water, had to be designed. This is the process of this invention, which is already patented. See, e.g., parent U.S. Patent No. 6,046,322. Because of this process, for the first time, it is now possible to achieve the purity of fludarabine-phosphate of 99.5% or greater, the currently used product purity in the FDA approved Fludara® commercial drug. Previously such an achievement was not possible. This new process can also be used for the purification of multi kilogram quantities of fludarabine-phosphate giving the same high purity of the product independent of the scale.

I hereby declare that all statements made herein of my own knowledge are true and that all statements were made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

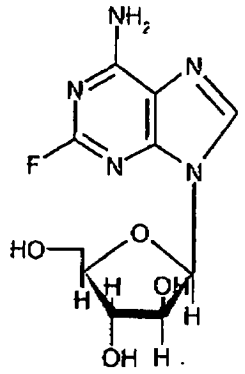
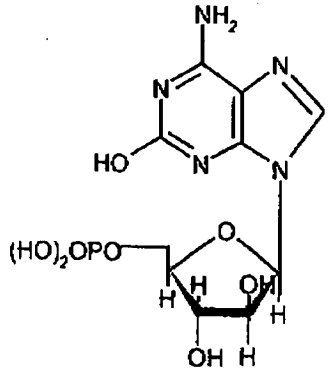
28/07/03

Date

Ulf Tilstam

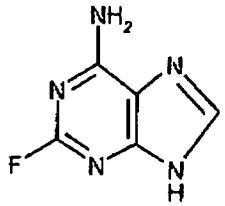
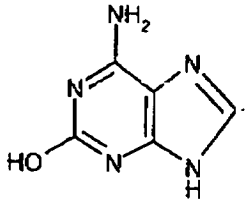
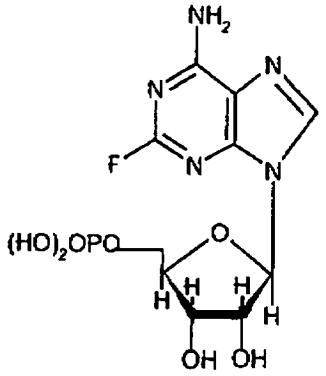
JER/jqs/jmj
K:\Sch\1615\D1\Declaration 5-29-03.doc

ATTACHMENT A
APP. NO. 09/471,040

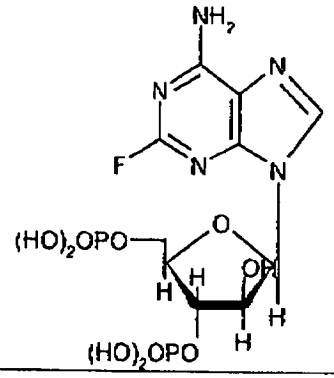
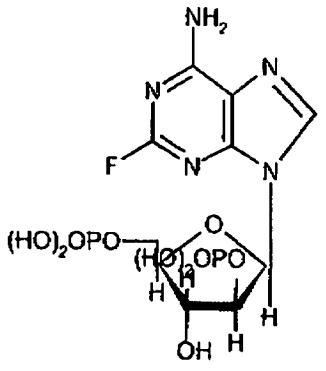
Compound No.	Structure	Chemical name according to IUPAC	Impurity content				
			< 98% pure fludarabine-phosphate	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
1		2-Fluoro-9-(ß-D-arabinofuranosyl)-9H-purin-6-amine	0,14	0,01	0,02	0,01	0,01
2		6-Amino-9(5-O-phosphono-ß-D-arabinofuranosyl)-9H-purin-2-ol	1,38	0,38	0,11	0,09	0,12

*inventive fludarabine-phosphate

ATTACHMENT A
APP. NO. 09/4[illegible],040

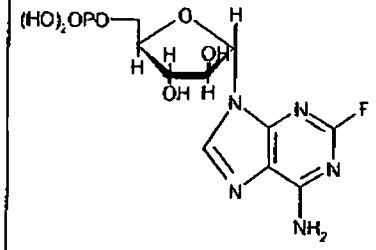
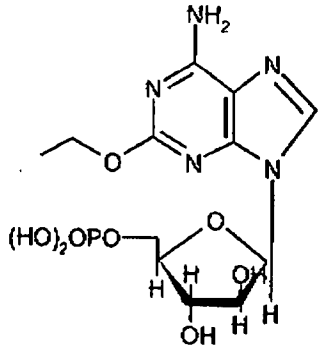
Compound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			< 98% pure fludarabine-phosphate	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
3		2-Fluoro-9H-purin-6-amine	0,03	0,05	0,02	0,02	0,02
4		6-Amino-9H-purin-2-ol	0,25	0,02	<0,02	0,02	<0,02
5		2-Fluoro-9-(5-O-phosphono-ß-D-arabinofuranosyl)-9H-purin-6-amine	0,02	0,02	0,04	0,03	0,05

*inventive fludarabine-phosphate

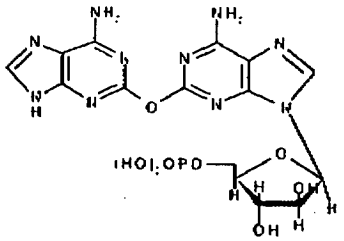
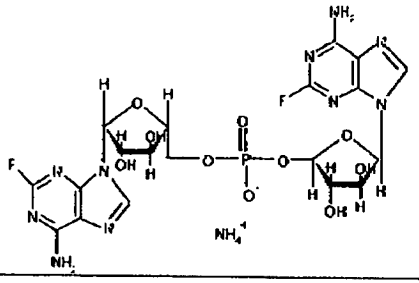
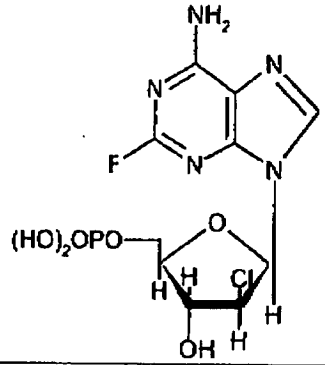
Compound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			< 98% pure fludarabine-phosphate	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
6		9-(3,4-O-Diphosphono-ß-D-arabinofuranosyl)-2-fluoro-9H-purin-6-amine	0,06	0,06	0,1	0,09	0,08
7		9-(2,5-O-Diphosphono-ß-D-arabinofuranosyl)-2-fluoro-9H-purin-6-amine	0,03	0,02	0,1	0,09	0,08

*inventive fludarabine-phosphate

ATTACHMENT A
APP. NO. 09/471,040

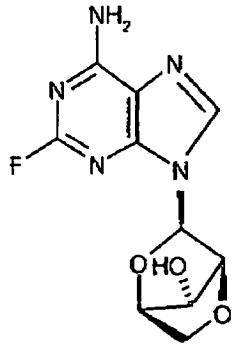
Compound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			< 98% pure fludarabine-phosphate	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
8		2-Fluoro-9-(5-O-phosphono-α-D-arabinofuranosyl)-9H-purin-6-amine	0,02	0,01	<0,02	<0,02	<0,02
9		2-Ethoxy-9-(5-O-phosphono-ß-D arabinofuranosyl)-9H-purin-6-amine	0,26	0,02	0,06	0,01	0,01

*inventive fludarabine-phosphate

Compound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			< 98% pure Fludarabine-phosphate	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
10		2-(6-Amino-9H-purin-2-yl)-9-(5-O-phosphono-ß-D-arabinofuranosyl)-9H-purin-6-amine	0,05	0,14	0,02	0,02	0,02
11		O,O'-Bis[2-(6-amino-2-fluoro-9H-purin-9-yl)-5-deoxy-b-D-arabinofuranos-5-yl]phosphate, Ammonium salt					
12		9-(2-Chloro -2-deoxy-5-phosphono-ß-D-arabinofuranosyl)-2-fluoro-9H-purin-6-amine	0,05	0,01	0,06	0,03	0,1

*Inventive fludarabine-phosphate

ATTACHMENT A
APP. NO. 09/471,040

Compound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			< 98% pure Fludarabine-phosphate	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
13		9-(2,5-O-Anhydro-ß-D-arabinofuranosyl)-2-fluoro-9H-purin-6-amine	0,04	0,12	0,06	0,03	0,1
Complete Impurities			2,33	0,86	<0,63	<0,43	<0,63

*inventive fludarabine-phosphate

Result:

- Commercial produced fludarabine-phosphate: max. 97,67% pure fludarabine-phosphate
- Ion exchange purification: max 99,14% pure fludarabine-phosphate
  (using commercially produced fludarabine-phosphate)
- fludarabine-phosphate produced via the disclosed process, using the di-sodium salt >99,37% up to >99,57% pure fludarabine-phosphate

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Offenlegungsschrift**

(10) **DE 195 43 052 A1**

(51) Int. Cl.[6]:
C 07 H 19/20
C 07 H 1/06

(21) Aktenzeichen: 195 43 052.2
(22) Anmeldetag: 6. 11. 95
(43) Offenlegungstag: 7. 5. 97

DE 195 43 052 A1

(71) Anmelder:
Schering AG, 13353 Berlin, DE

(72) Erfinder:
Tilstam, Ulf, Dr., 13359 Berlin, DE; Schmitz, Thomas, Dr., 10997 Berlin, DE; Nickisch, Klaus, Dr., 12307 Berlin, DE

(56) Entgegenhaltungen:
US 43 57 324

Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Verfahren zur Herstellung und Reinigung von Fludarabin-Phosphat und die Verwendung von sauren Ionenaustauschern im Verfahren

(57) Die Erfindung betrifft ein Verfahren zur Herstellung und Reinigung von Fludarabinphosphat und die Verwendung von sauren Ionenaustauschern im Verfahren.

DE 195 43 052 A1

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

BUNDESDRUCKEREI 03. 97 702 019/406 3/23

Beschreibung

Die Erfindung betrifft ein Verfahren zur Herstellung und Reinigung von Fludarabinphosphat und die Verwendung von sauren Ionenaustauschern zur Herstellung und Reinigung von Fludarabin-phosphat.

Fludarabin-phosphat ist der "International Nonproprietary Name" (INN) von 9H-Purin-6-amino-2-fluor-9-(5-0-phosbono-β-D-arabinofuranosyl)-dihydrogenphosphat. Die erste Synthese der Vorstufe des Fludarabin-phosphat, dem 9-β-D-Arabinofuranosyl -2-fluroadenin wird in US-PS 4,188,378 beschrieben. Diese Substanz weist stark cytotoxische Eigenschaften auf und es wurden verschiedene Derivate davon, mit dem Ziel der Reduzierung von Nebenwirkungen, hergestellt. Innerhalb der US-PS 4,357,324 wird das 5'- Phosphat (Prodrug), also das Fludarabin-phosphat und dessen Herstellung beschrieben. In weiteren Schriften, beispielsweise US-PS 4,210,745, WO 91/08215, WO94/12514 und DE 41 41 454 A1, werden alternative Herstellungsverfahren beschrieben.

Der derzeit benutzte Herstellungsweg geht von 9-β-D-Arabinofuranosyl -2-fluroadenin aus, das mit Trimethylphosphat und Phosphoroxychlorid umgesetzt wird (Phosphorylisierung). Diese Edukte werden umgesetzt und anschließend aus Wasser kristallisiert. Die bei der Umkristallisation anzuwendende Temperatur von etwa 75°C zerstört einen Teil der Substanz, da Fludarabin-phosphat bei dieser Temperatur thermisch instabil ist. Nachteilig ist weiter, daß diese aus dem Stand der Technik bekannte Umkristallisation nur zu einer schwachen Verbesserung der Reinheit führt und das Verfahren nur in kleinen Ansatzgrößen.

Aufgabe der vorliegenden Erfindung ist ein verbessertes Herstellungs- und Reinigungsverfahren bereitzustellen, welches zu einer deutlich verbesserten Qualität von Fludarabin-phosphat führt und was im großtechnischen Verfahren problemlos auch auf große Mengen angewendet werden kann.

Gelöst wird diese Aufgabe gemäß der Lehre der Patentansprüche.

Das beschriebene Verfahren zur Herstellung und Reinigung von Fludarabin-phosphat geht vom Rohprodukt aus, daß durch Umsetzung von 9-β-D-Arabinofuranosyl-2-fluroadenin mit Trimethylphosphat und Phosphoroxychlorid erhalten wird. Dieses Rohprodukt wird durch Umkristallisation aus entsalztem Wasser, bei Anwesenheit von 20—200 Gewichtsprozent eines sauren, kationischen Ionenaustauscher bezogen auf die eingesetzte Menge Fludarabin-phosphat und gegebenenfalls Zusatz von Aktivkohle umkristallisiert.

Mit Vorteil erfolgt die Umkristallisation bei Temperaturen von 70—90°C, vorzugsweise 85—90°C, mit besonderem Vorteil bei 88°C.

Als zu verwendende saure, kationische Ionenaustauscher eignen sich beispielsweise Amberlite, Duolite, IRC 50, Dowex oder deren Gemische davon.

Bei der Anwendung des erfindungsgemäßen Verfahrens erhält man Fludarabin in einer deutlich verbesserten Qualität und mit einer Gesamtausbeute von über 70%.

Die nachfolgenden Beispiele sollen die Erfindung näher erlautern:

BEISPIEL 1

10,0 g (27,4 mmol) Fludarabin-phosphat wird in 150 ml Wasser bei 88°C gelöst und heiß filtriert. Die

klare Lösung wird auf Raumtemperatur abgekühlt und 3 Tage gerührt, um aus dem Gel ein Kristallisat zu erhalten, anschließend wird abgesaugt und mit Wasser und Ethanol gewaschen. Das erhaltene Kristallisat wird getrocknet, 6,0 g (60% d.Th.).

BEISPIEL 2

10,0 g (27,4 mmol) Fludarabin-phosphat wird in 150 ml Wasser bei 88°C gelöst und 15 g Ionenaustauscher A252 C werden zugegeben. Die Lösung mit dem Tauscher wird 8 Min. gerührt und anschließend schnell filtriert. Die klare Lösung wird auf Raumtemperatur abgekühlt. Die Kristallsuspension wird über Nacht bei RT stehengelassen, anschließend wird abgesaugt und das Kristallisat mit Wasser und Ethanol gewaschen. Nach der Trocknung erhält man 5,4 g (54% d.Th.).

BEISPIEL 3

10,0 g (27,4 mmol) Fludarabin-phosphat wird in 150 ml Wasser bei 88°C gelöst und 15 g Ionenaustauscher A252 C und 2 g Aktiv Kohle werden zugegeben. Die Mischung wird 8 Min. gerührt und anschließend schnell filtriert. Die klare Lösung wird auf Raumtemperatur gekühlt. Die Kristallsuspension wird über Nacht bei RT stehengelassen, anschließend wird abgesaugt und das Kristallisat mit Wasser und Ethanol gewaschen. Nach der Trocknung erhält man 5,0 g (50% d.Th.).

BEISPIEL 4

10,0 g (27,4 mmol) Fludarabin-phosphat wird in 150 ml Wasser bei 88°C gelöst und 15 g Ionenaustauscher Duolite CU 33 wird zugegeben. Die Lösung mit dem Tauscher wird 8 Min. gerührt und anschließend schnell filtriert. Die klare Lösung darf von alleine auf Raumtemperatur kommen. Die Kristallsuspension wird über Nacht bei RT stehengelassen, anschließend wird abgesaugt und das Kristallisat mit Wasser und Ethanol gewaschen. Nach der Trocknung erhält man 5,2 g (52% d.Th.).

BEISPIEL 5

20,0 g (54,8 mmol) Fludarabin-phosphat wird in 150 ml Wasser bei 88°C gelöst und 4 g Ionenaustauscher IRC 50 zugegeben. Die Lösung mit dem Tauscher wird 8 Min. gerührt und anschließend schnell filtriert. Die klare Lösung darf von alleine auf Raumtemperatur kommen. Die Kristallsuspension wird über Nacht bei RT stehengelassen, anschließend wird abgesaugt und das Kristallisat mit Wasser und Ethanol gewaschen. Nach der Trocknung erhält man 14,4 g (72% d.Th.).

BEISPIEL 6

10,0 g (27,4 mmol) Fludarabin-phosphat wird in 150 ml Wasser + 88°C gelöst und 2 g Ionenaustauscher AXAD-7 wird zugegeben. Die Lösung mit dem Tauscher wird 8 Min. gerührt und anschließend schnell filtriert. Die klare Lösung darf von alleine auf Raumtemperatur kommen. Die Kristallsuspension wird über Nacht bei RT stehengelassen, anschließend wird abgesaugt und das Kristallisat mit Wasser und Ethanol gewaschen. Nach der Trocknung erhält man 7,4 g (74% d.Th.).

BEISPIEL 7

10,0 g (27,4 mmol) Fludarabin-phosphat wird in 150 ml Wasser + 88°C gelöst und 15 g Ionenaustauscher Dowex SOX2-200 wird zugegeben. Die Lösung mit dem Tauscher wird 8 Min. gerührt und anschließend schnell filtriert. Die klare Lösung darf von alleine auf Raumtemperatur kommen. Die Kristallsuspension wird über Nacht bei RT stehengelassen, anschließend wird abgesaugt und das Kristallisat mit Wasser und Ethanol gewaschen. Nach der Trocknung erhält man 6,5 g (65% d.Th.).

Patentansprüche

1. Verfahren zur Herstellung und Reinigung von Fludarabin-phosphat aus 9-β-D-arabinofuranosyl-2-fluoroadenin, Trimethylphosphat und Phorphoroxychlorid, dadurch gekennzeichnet, daß das erhaltene feste Reaktionsprodukt (Kristallisat) aus entsalzten Wasser bei Anwesenheit von 20—200 Gew.% sauren, kationischen Ionenstauscher, bezogen auf die eingesetzte Menge Fludarabin-phosphat und gegebenenfalls Aktivkohle, umkristallisiert wird.
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Umkristallisation bei Temperaturen von 70—90°C durchgeführt wird.
3. Verfahren nach den Ansprüchen 1 und 2, dadurch gekennzeichnet, daß als saurer Ionenaustauscher Amberlite, Duolite, ICR 50, Dowex oder Gemische davon verwendet werden.
4. Verwendung von sauren Ionenaustauscher zur Herstellung und Reinigung von Fludarabin-phosphat.

VERIFICATION OF TRANSLATION

I, Melissa Stanford, a translator with Chillson Translating Service, 3530 Chas Drive, Hampstead, Maryland, 21074, hereby declare as follows:

That I am familiar with the German and English languages;

That I am capable of translating from German to English;

That the translation attached hereto is a true and accurate translation of German Application 195 43 052.2 titled, "Process for the Production and Purification of Fludarabine Phosphate and the Use of Acidic Ion Exchangers in the Process;"

That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

And further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any registration resulting therefrom.

By Melissa Stanford

Executed this 3 day of July 2003.

Witness Anne Chillson

(19) **FEDERAL REPUBLIC OF GERMANY**

GERMAN PATENT OFFICE

(12) **Laid-Open Specification**

(10) **DE 195 43 052 A 1**

(21) File number: 195 43 052.2

(22) Application date: 11/6/95

(43) Date laid open: 5/7/97

(51) Int. Cl.[6]:

C 07 H 19/20

C 07 H 1/06

(71) Applicant:

Schering AG, 13353 Berlin, DE

(72) Inventors:

Tilstam, Ulf, Dr., 13359 Berlin, DE: Schmitz, Thomas, Dr., 10997 Berlin, DE;

Nickisch, Klaus, Dr., 12307 Berlin, DE

(55) Citations:

US 43 57 324

The request for examination according to §44 of the Patent Law has been made

(54) Process for the Production and Purification of Fludarabine Phosphate and the Use of Acidic Ion Exchangers in the Process

(57) The invention relates to a process for the production and purification of fludarabine phosphate and the use of acidic ion exchangers in the process.

The following information is taken from the documents filed by the applicant. 3/23

FEDERAL PRINTING OFFICE 3/97 702 019/406

DE 195 43 052 A1

Description

The invention relates to a process for the production and purification of fludarabine phosphate and the use of acidic ion exchangers for the production and purification of fludarabine phosphate.

Fludarabine phosphate is the "International Nonproprietary Name" (INN) of 9H-purine-6-amino-2-fluoro-9-(5-0-phosphono-β-D-arabinofuranosyl)-dihydrogen-phosphate. The first synthesis of the precursor of fludarabine phosphate, the 9-β-D-arabinofuranosyl-2-fluoroadenine, is described in US-PS 4,188,378. This substance exhibits strong cytotoxic properties, and various derivatives of it were produced with the purpose of reducing side effects. Within US-PS 4,357,324, the 5'-phosphate (prodrug), i.e., the fludarabine phosphate and its production, is described. In further publications, for example US-PS 4,210,745, WO 91/08215, WO 94/12514 and DE 41 41 454 A1, alternative production processes are described.

The production method that is now used starts from 9-β-D-arabinofuranosyl-2-fluoroadenine, which is reacted with trimethyl phosphate and phosphorus oxychloride (phosphorylation). These educts are reacted and then crystallized from water. The temperature of about 75°C that is to be used in the recrystallization destroys a portion of the substance, since fludarabine phosphate is thermally unstable at this temperature. It is further disadvantageous that this recrystallization that is known from the prior art results only in a weak improvement of purity and the process results only in small batch sizes.

The object of this invention is to provide an improved production and purification process that results in a considerably improved quality of fludarabine phosphate and that in an industrial-scale process can also be applied even to large amounts.

This object is achieved according to the teaching of the claims.

The described process for the production and purification of fludarabine phosphate starts from the crude product that is obtained by reaction of 9-β-D-arabinofuranosyl-2-fluoroadenine with trimethyl phosphate and phosphorus oxychloride. This crude product is recrystallized by recrystallization from demineralized water in the presence of 20-200% by weight of an acidic, cationic ion exchanger relative to the amount of fludarabine phosphate that is used and optionally the addition of activated carbon.

The recrystallization advantageously is carried out at temperatures of 70-90°C, preferably 85-90°C, especially advantageously at 88°C.

As acidic, cationic ion exchangers that are to be used, for example, Amberlite, Duolite, IRC 50, Dowex, or mixtures thereof are suitable.

When using the process according to the invention, fludarabine is obtained in a considerably improved quality and with a total yield of over 70%.

The following examples are to explain the invention in more detail.

EXAMPLE 1

100 g (27.4 mmol) of fludarabine phosphate is dissolved in 150 ml of water at

88°C and hot-filtered. The clear solution is cooled to room temperature and stirred for 3 days to obtain a crystallizate from the gel, then it is suctioned off and washed with water and ethanol. The crystallizate that is obtained is dried, 6.0 g (60% of theory).

EXAMPLE 2

10.0 g (27.4 mmol) of fludarabine phosphate is dissolved in 150 ml of water at 88°C, and 15 g of ion exchanger A252 C is added. The solution is stirred with the exchanger for 8 minutes and then quickly filtered. The clear solution is cooled to room temperature. The crystal suspension is allowed to stand overnight at room temperature, then it is suctioned off, and the crystallizate is washed with water and ethanol. After drying, 5.4 g (54% of theory) is obtained.

EXAMPLE 3

10.0 g (27.4 mmol) of fludarabine phosphate is dissolved in 150 ml of water at 88°C, and 15 g of ion exchanger A252 C and 2 g of activated carbon are added. The mixture is stirred for 8 minutes and then quickly filtered. The clear solution is cooled to room temperature. The crystal suspension is allowed to stand overnight at room temperature, then it is suctioned off, and the crystallizate is washed with water and ethanol. After drying, 5.0 g (50% of theory) is obtained.

EXAMPLE 4

10.0 g (27.4 mmol) of fludarabine phosphate is dissolved in 150 ml of water at 88°C, and 15 g of ion exchanger Duolite CU 33 is added. The solution is stirred with the

exchanger for 8 minutes, and then it is quickly filtered. The clear solution must come to room temperature by itself. The crystal suspension is allowed to stand overnight at room temperature, then it is suctioned off, and the crystallizate is washed with water and ethanol. After drying, 5.2 g (52% of theory) is obtained.

EXAMPLE 5

20.0 g (54.8 mmol) of fludarabine phosphate is dissolved in 150 ml of water at 88°C, and 4 g of ion exchanger IRC 50 is added. The solution is stirred with the exchanger for 8 minutes and then quickly filtered. The clear solution must come to room temperature by itself. The crystal suspension is allowed to stand overnight at room temperature, then it is suctioned off, and the crystallizate is washed with water and ethanol. After drying, 14.4 g (72% of theory) is obtained.

EXAMPLE 6

10.0 g (27.4 mmol) of fludarabine phosphate is dissolved in 150 ml of water + 88°C, and 2 g of ion exchanger AXAD-7 is added. The solution is stirred with the exchanger for 8 minutes and then quickly filtered. The clear solution must come to room temperature by itself. The crystal suspension is allowed to stand overnight at room temperature, then it is suctioned off, and the crystallizate is washed with water and ethanol. After drying, 7.4 g (74% of theory) is obtained.

EXAMPLE 7

10.0 g (27.4 mmol) of fludarabine phosphate is dissolved in 150 ml of water + 88°C, and 15 g of ion exchanger Dowex SOX2-200 is added. The solution is stirred with the exchanger for 8 minutes and then quickly filtered. The clear solution must come to room temperature by itself. The crystal suspension is allowed to stand overnight at room temperature, then it is suctioned off, and the crystallizate is washed with water and ethanol. After drying, 6.5 g (65% of theory) is obtained.

CLAIMS

1. Process for the production and purification of fludarabine phosphate that consists of 9-β-D-arabinofuranosyl-2-fluoroadenine, trimethyl phosphate and phosphorus oxychloride, characterized in that the solid reaction product that is obtained (crystallizate) is recrystallized from demineralized water in the presence of 20-200% by weight of an acidic, cationic ion exchanger, relative to the amount of fludarabine phosphate that is used and optionally activated carbon.
2. Process according to claim 1, wherein the recrystallization is performed at temperatures of 70-90°C.
3. Process according to claims 1 and 2, wherein as acidic ion exchangers, Amberlite, Duolite, ICR 50, Dowex or mixtures thereof are used.
4. Use of acidic ion exchanger for the production and purification of fludarabine phosphate.